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Pre-pregnancy overweight or obesity and gestational diabetes as predictors of body composition in offspring twenty years later – evidence from two birth cohort studies

Short title: Maternal obesity and GDM size up adult offspring

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ABSTRACT

BACKGROUND: Global prevalence of overweight/obesity and gestational diabetes (GDM) is increasing. In pregnant women both conditions affect offspring's later health. Overweight/obesity is a risk factor of GDM; to what extent maternal overweight/obesity explains long-term effects of GDM in offspring is unknown.

OBJECTIVE: To evaluate effects of maternal pre-pregnancy overweight/obesity (BMI ≥25kg/m^2) and GDM, occurring together or separately, on body composition among adult offspring.

METHODS: Participants include 891 individuals aged 24.1 years (SD 1.4) from two longitudinal cohort studies (ESTER and AYLS). Adult offspring of normoglycemic mothers with overweight/obesity (ONOO, n=153), offspring of mothers with GDM (OGDM; n=191) and controls (n=547) underwent anthropometric measurements and bioimpedance analysis. GDM was diagnosed by oral glucose tolerance test. Data were analyzed by linear regression models adjusted for confounders.

RESULTS: Compared with controls, ONOO-participants showed higher BMI [men 1.64kg/m^2 (95% confidence interval 0.57, 2.72); women 1.41kg/m^2 (0.20, 2.63)] and fat percentage [men 2.70% (0.99, 4.41); women 2.98% (0.87, 5.09)] with larger waist circumferences [men 3.34cm (0.68, 5.99); women 3.09cm (0.35, 5.83)]. Likewise, OGDM-participants showed higher fat percentage [men 1.97% (0.32, 3.61); women 2.32% (0.24, 4.41)]. BMI was non-significantly different between OGDM-participants and controls [men 0.88kg/m^2 (-0.17, 1.92); women 0.82kg/m^2 (-0.39, 2.04)]. Also waist circumferences were larger [men 2.63cm (-0.01, 5.28); women 3.39cm (0.60, 6.18)], this difference was statistically significant in OGDM-women only. Differences in body composition measures were stronger among offspring of women with both GDM and overweight/obesity. For instance, fat mass was

higher among OGDM-participants of overweight mothers [men 4.24kg (1.36, 7.11) vs. controls; women 5.22kg (1.33, 9.11)] than OGDM participants of normal weight mothers [men 1.50kg (-2.11, 5.11) higher vs. controls; women 1.57kg (-3.27, 6.42)].

CONCLUSIONS: Maternal pre-pregnancy overweight and GDM are associated with unhealthy body size and composition in offspring over 20 years later. Effects of maternal pre-pregnancy overweight appear more pronounced.

INTRODUCTION

The rising incidence of obesity is a major public health problem worldwide and obesity is officially recognized as a disease by the World Health Organization (WHO) (1). Much of the increase in overweight (body mass index, BMI ≥ 25kg/m^2) and obesity (BMI ≥ 30kg/m^2) is due to increasing physical inactivity and unhealthy diet (2). In addition, dietary excess, poverty, feminine gender, environmental factors, socioeconomic status and inequalities in educational status are factors associated with overweight/obesity (3). The increased rates of overweight account for an increase in the global burden of cardiometabolic diseases and risk factors, such as high blood pressure and high plasma glucose. In addition, other factors, such as individual phenotype differences resulting from e.g. epigenetic changes caused by early life adversities, may add to this increase in both overweight/obesity and cardiometabolic diseases. Examples of such early life adversities include intrauterine exposure to gestational diabetes mellitus (GDM) or maternal overweight or obesity. Prenatal exposure to a hyperglycemic environment alters growth trajectories and homeostatic regulatory mechanisms, predisposing the offspring to epigenetic changes (4), which may cause an increased risk of next-generation overweight and obesity through fetal programming.

Maternal obesity has consequences for the offspring's later health, particularly an increased risk for obesity and metabolic sequelae (5). Studies have linked high maternal pre-pregnancy BMI with unfavorable offspring body composition in infancy (6), childhood (7) and adolescence (8). However, it is unclear if GDM, a key comorbidity of overweight/obesity, is an independent risk factor for offspring overweight in adulthood. This would have consequences on whether to direct prevention of offspring risks to preventing maternal overweight/obesity or also to prevent and treat GDM. Previous studies have shown that

offspring to mothers with GDM have a higher BMI and waist circumference at adolescence than offspring of mothers without GDM (9). Despite previously well-established data on the strong influence of maternal pre-pregnancy overweight or GDM on offspring's increased risk for obesity and metabolic sequelae during childhood, it is less clear whether the effects extend into adult age.

We assessed body composition in the offspring entering their third decade. We hypothesized that adult offspring of mothers with pre-pregnancy overweight/obesity or GDM have unhealthier body size and composition, compared with controls not exposed to these pregnancy conditions. Further, we hypothesized that simultaneous exposure to both of these conditions causes more pronounced effects on offspring body composition.

MATERIALS AND METHODS

Study population

The participants of the current study come from two prospective birth cohorts (Figure 1): the ESTER Maternal Pregnancy Disorders Study and the Arvo Ylppö Longitudinal Study (AYLS).

The ESTER Study consists of two arms: ESTER Preterm Birth (10) and ESTER Maternal Pregnancy Disorders arms; our present report is based on the latter arm. All ESTER study participants were born in the two northernmost provinces of Finland; those born in 1985–1986 were recruited from the Northern Finland Birth Cohort 1986 (NFBC 1986) (11) and those born in 1987–1989 through the Finnish Medical Birth Register (FMBR) (10), as previously described (Figure 1). We selected all participants of the ESTER Maternal Pregnancy Disorders arm who were invited for maternal GDM (n=157). Among ESTER clinical study participants invited as controls, participants were classified into two groups: one

group with maternal pre-pregnancy overweight/obesity included offspring born at term with maternal pre-pregnancy BMI ≥ 25kg/m^2 and no GDM (n=44), while the control group constituted the remaining controls, all with maternal BMI < 25kg/m^2 and no GDM (n=281). The AYLS participants (Figure 1) were born in the province of Uusimaa, in Southern Finland between 1985 and 1986. This cohort consists of all liveborn infants admitted to neonatal wards in obstetric units, or transferred to the neonatal intensive care unit of the Children's Hospital, Helsinki University Central Hospital within 10 days of their birth, with the population ranging from severely ill preterm infants to infants born at term requiring only brief inpatient observation and their controls, as previously described in detail (12, 13). Of these AYLS cohort participants, we selected all those who were exposed to maternal GDM, regardless of maternal BMI (n=37), and those who had maternal BMI ≥ 25kg/m^2 and no GDM (n=109), and controls (originally recruited as controls, maternal BMI < 25kg/m^2 and no GDM; n=266).

Perinatal data were collected from healthcare records and questionnaires for both ESTER and AYLS cohort participants. Length of gestation, maternal GDM, hypertension (gestational or chronic) and preeclampsia (including superimposed) diagnoses (according to prevailing criteria) were independently confirmed by reviewing original hospital records (9,14). Maternal GDM was diagnosed by oral glucose tolerance test (OGTT). Screening for GDM by OGTT was performed in the maternal welfare clinics between 26 and 28 gestational weeks. Indications for screening were glucosuria, prior GDM, suspected fetal macrosomia, previous macrosomic infant (birth weight >4,500 g), maternal pre-pregnancy BMI ≥ 25 kg/m^2, and maternal age ≥ 40 years. The OGTT was performed after overnight fasting by using a 75-g oral glucose load. According to prevailing national guidelines, at the time of diagnosis in the 1980s, the following cutoff limits for GDM were used for venous blood glucose: >5.5 mmol/l

at fasting, >11.0 mmol/l and >8.0 mmol/l, 1 hour and 2 hours after the glucose load, respectively. A diagnosis of GDM was made with one abnormal value in the OGTT (9). For comparison, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) Consensus Panel diagnostic criteria used today are set at fasting plasma glucose ≥5.1mmol/l, and ≥10.0 mmol/l and ≥8.5 mmol/l following a 75g oral glucose load (15). Among mothers with GDM from the ESTER cohort, 21 were treated with insulin and 40 with guargum, while the remaining mothers were treated with diet only. From the AYSL cohort 31 mothers with GDM were treated with insulin. For the AYLS cohort mothers' data on guargum treatment has not been collected.

Offspring to mothers with type 1 (n=28) or 2 diabetes (n=1) were not included in the analyses. We further excluded subjects who were pregnant (n=9) during the clinical examination, reported having cerebral palsy (n=8), mental disability (n=11) or severe physical disability (n=5) from the analyses, as these conditions likely affect body composition. We categorized all ESTER and AYLS cohort participants who underwent bioelectrical impedance analysis (BIA) into three groups: 1) offspring of normoglycemic mothers with pre-pregnancy overweight or obesity (ONOO), 2) offspring of mothers with GDM (OGDM) at any level of maternal BMI and 3) controls, i.e. offspring of mothers with pre-pregnancy BMI < 25kg/m^2 and no GDM. As a result, 891 subjects were included in the analyses; ONOO n= 153, OGDM n= 191 and 547 controls.

Ethics

Study protocol was in accordance with the Declaration of Helsinki and approved by the Ethics Committees of the University of Oulu, the Helsinki City Maternity Hospital, the

Helsinki University Central Hospital and Jorvi Hospital, the Ethics Committee of the Northern Ostrobothnia Hospital District and the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District. Written informed consent was obtained from all participants. Because of individual participant consent, the data are not freely available to readers. Researchers requesting data access are asked to contact the corresponding author. Requests may be subject to ethics review and/or participant reconsent.

Measures and procedures

During clinical examinations, conducted in 2009-2011 for ESTER participants, and in 2009-2012 for AYLS participants, anthropometry was measured. Height was measured three times without socks and shoes, with a portable stadiometer and waist circumference (midway between the lowest rib and the iliac crest) was measured twice, means of the results were used in the analyses (16). BMI was calculated using means of the repeated measurements [weight (kg) / height squared (m^2)]. We measured body composition (weight, lean body mass (LBM), fat mass and percentage body fat) by segmental multifrequency bioelectrical impedance analysis (BIA; InBody 3.0, Biospace Co., Ltd., Seoul, Korea). BIA reliably calculates body composition by measuring resistance to an imperceptible electrical current passed through the body (17-19). Water is a good conductor of electrical current and BIA differentiates between lean tissue and fat tissue based on their different water contents, i.e. calculates body composition based on differences in resistance to the electrical flow in the different tissues.

All participants completed questionnaires regarding health status, including medical history and medications. We used parental educational attainment, categorized into four levels (dummy coded), as an indicator of childhood socioeconomic status.

Statistical analyses

All statistical analyses were conducted with IBM SPSS Statistics versions 22 and 24 (SPSS Inc., Chicago, IL, USA). This was a cohort study and the power of sample size is indicated by confidence intervals. Outcome data were normally distributed. To estimate variation within each group of data we describe SDs. The significance level was set to two-tailed $P < 0.05$. We compared descriptive characteristics between participants with *t*-test (continuous variables) and χ^2-test (categorical variables). We used linear regression models to compare measures of body size and composition between the adult offspring of mothers with pre-pregnancy overweight or GDM and controls. We adjusted for age and birth cohort in model 1; and for age, birth cohort, gestational age, birth weight SD score, maternal hypertension or preeclampsia during pregnancy, maternal smoking during pregnancy and parental educational attainment in model 2. Because body composition in adults is a sexually dimorphic trait, we present all results for men and women separately. Analyses were performed in a combined dataset of both birth cohorts (ESTER and AYLS). We also report analyses performed in each cohort. In the OGDM-group, we also ran all analyses separately comparing offspring of GDM mothers with pre-pregnancy BMI < 25 kg/ m^2 and offspring of GDM mothers with pre-pregnancy BMI ≥ 25 kg/m^2 with controls. In a subgroup with data available on paternal BMI, we reran models 1 and 2, with additional adjustment for paternal BMI, calculated based on height and weight reported by the offspring.

RESULTS

Perinatal and current characteristics of mothers and offspring are presented in Table 1. Mean age of offspring at assessment was 24.1 years (SD 1.4) and 51% were women. Among offspring, 2 OGDM, 2 OONO and 8 controls were born from twin pregnancies, the remaining offspring were all singletons. Current body size and body composition of the offspring are shown in Table 2. Data for the two birth cohort studies are presented separately (Tables 1, 2 and Supplementary Table 1). For comparison, corresponding mean values in the general Finnish population (20) or reference values are also shown (Table 2).

Body size and composition in offspring of overweight or obese mothers

There were clear associations between maternal pre-pregnancy overweight/obesity and adult offspring body size and composition. While ONOO-men and ONOO-women had similar heights as their controls, ONOO-men and -women had higher BMI, waist circumference, fat mass and fat percentage than control men and women (Table 3). Additional adjustment for paternal BMI did not change the results in men. Among women, the results slightly attenuated in the subgroup with data available and height was shorter (Supplementary Table 2).

Body size and composition in offspring of mothers with gestational diabetes

Among OGDM-men, mean height and LBMs were similar to the controls (Table 3). Their BMI and waist circumferences were slightly higher, although not reaching statistical significance. Fat mass and fat percentages were both higher in OGDM-men than in controls (Table 3). In OGDM-women, both waist circumferences and fat percentages were significantly higher than in controls, while BMIs, LBMs and fat mass all were non-significantly higher compared

with controls. As with men, also among OGDM-women, height was similar to the controls (Table 3).

In the subgroup with data on paternal BMI, OGDM-men showed larger waist circumferences, in addition to higher fat mass and fat percentage, while among women the results slightly attenuated (Supplementary Table 2).

Body size and composition in offspring of normal weight or overweight mothers with gestational diabetes

To examine whether the association between GDM and adult offspring body composition is attributable to maternal pre-pregnancy overweight/obesity, we performed more detailed analyses within the OGDM-group. First we repeated all analyses in a subgroup comparing offspring of GDM mothers with normal weight (n=117) with controls (Table 4). In both men and women waist circumference was larger in offspring of GDM mothers, although this finding reached statistical significance only in model 1, adjusted for age and cohort. Other measures of body size and composition were similar between the study groups. When offspring of GDM mothers with overweight (n=72) were compared with controls, BMI, fat mass and fat percentage were all higher among offspring of GDM mothers with overweight. Further, among women, also waist circumference was higher in offspring of GDM mothers with overweigh, while male offspring were shorter than controls. For both men and women, LBM was higher in model 1, but this difference did not survive adjustment for confounders in model 2 (Table 4). Hence, the effect of maternal pre-pregnancy overweight or obesity on offspring body composition appeared greater than that of maternal GDM.

DISCUSSION

We combined data from two longitudinal birth cohorts to study body size and composition in the adult offspring to mothers with overweight or mothers with GDM. Our main finding was that pre-pregnancy overweight/obesity was associated with increased fat deposition in adult offspring, as measured by BIA. More specifically, BMI, waist circumference, fat mass and fat percentage were all found to be higher than in controls. As for offspring of mothers with GDM, compared with controls, waist circumference was significantly higher in women, fat mass was higher in men, and fat percentage was higher in both men and women in the fully adjusted model, which included pregnancy-related and socio-economic factors. In additional analyses, the associations were particularly pronounced in offspring of GDM women with overweight or obesity.

In line with our findings, high maternal pre-pregnancy BMI has been linked with unfavorable offspring body composition in infancy (6). Starling et al measured body composition in newborns at 3 days of age by air displacement plethysmography and each 1-kg/m^2 increase in maternal pre-pregnancy BMI was associated with a 5.2 g increase in neonatal fat mass, 7.7 g in fat-free mass and 0.12% in percentage of body fat (6). Similarly, a direct association of maternal pre-pregnancy BMI and childhood body composition measured by air displacement plethysmography at 6 years of age, has been described (for each 1-kg/m^2 of maternal pre-pregnancy BMI increase, 70 g in the offspring fat mass) (7). In our young adult offspring, each 1-kg/m^2 of maternal pre-pregnancy BMI increase corresponded with 270 g increase in fat mass in men and 150 g in women. Also at age 16 years, maternal pre-pregnancy overweight seems to be a risk factor for offspring overweight and abdominal obesity, independent of possible GDM (8). However, in that study the risk of offspring overweight and abdominal obesity was highest in offspring with concomitant prenatal

exposure to both maternal pre-pregnancy overweight and GDM (8). A further finding consistent with ours is from Reynolds et al., who found increased maternal BMI in pregnancy to be a predictor of greater adiposity in offspring at age 30 years (n=276) as measured by four-site skinfold thicknesses, waist circumference, and BMI (21). Highlighting the intergenerational effects of obesity, in one study higher maternal BMI was associated with less favorable body composition and higher BMI in the offspring even at a mean age of 62 years (22). Moreover, in the old age offspring, those whose mothers had a higher BMI, had higher rates of cancer, coronary heart disease, stroke and diabetes (23).

As for effects of GDM in offspring, in a large multinational cross-sectional study that included 4740 children, maternal GDM was associated with higher BMI, waist circumference and fat mass (measured by single frequency BIA) and increased odds of obesity at age 9-11 years, but most of these associations attenuated to non-significance when adjusted for current maternal BMI (24). In the 16- year follow-up of the Northern Finland Birth Cohort, one of the source cohorts of the present study, BMI, waist circumference and prevalence of overweight were higher in offspring to mothers with GDM (9). However, the increased odds for overweight and abdominal obesity were only seen in offspring of women with overweight/obesity and GDM; the offspring of women with normal weight and GDM had similar odds as controls (8). Although our study had limited power to separately assess offspring of women with normal weight and GDM or offspring of women with overweight/obesity and GDM, a conclusion from these studies is that much, if not most, of the higher adiposity in offspring of GDM mothers is due to maternal overweight or obesity. An important question is to what extent the consequences of these maternal characteristics are mediated through maternal hyperglycemia, because hyperglycemia is an accessible target of treatment. The distinction between the offspring into maternal overweight/obesity

and maternal GDM may not be helpful as women with overweight/obesity may have hyperglycemia even if they are not detected by OGTT, and women with GDM may be close to normoglycemic when adequately treated. Mothers with type 1 diabetes are more likely to have hyperglycemia and may serve as a model to answer this question. Clausen et al. compared 18-27-year-old offspring to mothers with diet-treated GDM and offspring of mothers with type 1 diabetes to control offspring. Interestingly, the odds for offspring overweight were 2-fold in both of these groups as compared with controls; the odds survived adjustment for maternal pre-pregnancy BMI (25). Although that study had no direct data on hyperglycemia comparable between T1D and GDM groups, these similar odds argue for a direct role of maternal hyperglycemia. As to complications of offspring adiposity, the risk for metabolic syndrome 4- and 2.5-fold increased in offspring of GDM and T1D women respectively, adjusted for maternal BMI (25).

The obesity epidemic has affected almost all age groups worldwide. Our study was conducted in Finland, where more than 55% of the adult Finnish population is overweight, as are 59% and 67% of the populations in Europe (WHO region) and the United States (26). Weight loss and maintenance is known to be extremely difficult, and this emphasizes the role of prevention. Our finding of enhanced fat deposition in offspring of mothers with overweight/obesity or GDM, point to an additional beneficial health effect from interventions during pregnancy, in both the target group of pregnant women and also in the next generation. Somewhat surprisingly, in a randomized controlled trial by Tanvig et al (27), lifestyle intervention in pregnancy did not result in changes in offspring anthropometrics at 2.8 years when comparing offspring of women with obesity with offspring of women with normal weight; offspring BMI, percentage of children with overweight/obesity, body composition (measured by DEXA) and anthropometric measurements were all similar

among the children. The authors speculated that perhaps participants of the intervention study were highly motivated to focus on a healthy lifestyle, diluting possible differences compared to the reference group.

Strengths of our study include availability of a long follow-up time with detailed and validated information on anthropometrics and body composition. Anthropometrics, i.e. height and waist circumference, were measured in the research center by trained staff instead of relying on self-reported information. Body composition was measured by BIA, shown reliable in different populations and for repeated measurements (17-19). Another strength of our study is a reasonable sample size. The participants come from the ethnically homogenous Finnish population, albeit from two different cohorts, and age, sex, pre- and postnatal factors were considered as potential confounders. Although residual confounding cannot be excluded, adjustment for important confounding factors (birth and perinatal characteristics, age and cohort) had little effect on the results.

Both treatment and GDM screening guidelines have changed during the previous 30 years. Therefore, the GDM offspring in the present study may represent the more severe end of the GDM spectrum in today's pregnant women. Further, we do not have data on maternal hyperglycemia during pregnancy. It is also of note that body size and composition are affected by a variety of reasons, e.g genes and epigenetic programming, as well as nutrition and lifestyle factors. Many mothers have most likely been overweight or obese after birth and throughout the childhood of the offspring. People with obesity eat differently and offer different food to their offspring, this effects offspring body composition. Postnatal environment, known to affect offspring BMI, was only taken into consideration in the present study by adjusting for highest parental education. Furthermore, we were unable to control for lifetime lifestyle.

To conclude, maternal pre-pregnancy overweight and obesity are associated with increased adiposity in adult offspring, placing them at increased risk for overweight, obesity and their sequelae later in adulthood. These sequelae may include increased cardiometabolic health risk, physical and psychosocial functioning. To some extent also maternal GDM effects adult offspring body composition, although this association is partly explained by maternal pre-pregnancy overweight and obesity.

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FIGURE LEGENDS:

Figure 1. Flow chart of the study population, including participants from two birth cohort studies.

Table 1. Baseline participant characteristics of adult offspring, exposed to maternal gestational diabetes, maternal pre-pregnancy obesity or overweight and their controls, i.e. offspring of normoglycemic mothers with normal pre-pregnancy weight. Data is shown by birth cohort.

	ESTER cohort (n=479)			AYLS cohort (n=412)		
Characteristic	Maternal gestational diabetes (n=154)	Maternal pre-pregnancy obesity or overweight[a] (n=44)	Control (n=281)	Maternal gestational diabetes (n=37)	Maternal pre-pregnancy obesity or overweight [a] (n=109)	Control (n=266)
Birth/Perinatal characteristics						
Maternal body mass index before pregnancy, mean (SD), kg/m^2	25.0 (5.8)	27.7 (1.9)	21.3 (1.8)	24.4 (3.9)	28.1 (3.4)	21.1 (1.9)
Twin pregnancy, n (%)	2 (1.3)	0 (0)	1 (0.4)	0 (0)	2 (1.8)	7 (2.6)
Maternal hypertension, n (%)	33 (21.4)	9 (20.5)	21 (7.5)	8 (21.6)	37 (33.9)	29 (10.9)
Maternal pre-eclampsia, n (%)	11 (7.1)	2 (4.5)	12 (4.3)	1 (2.7)	2 (1.8)	4 (1.5)
Maternal smoking during pregnancy, n (%)	17 (11.0)	11 (25.0)	45 (16.0)	6 (16.2)	22 (20.2)	45 (16.9)
Birth weight, mean (SD), g	3651 (601)	3703 (736)	3519 (466)	3881 (648)	3339 (901)	3555 (462)
Birth weight SD score, mean (SD)	0.48 (1.2)	0.27 (1.3)	-0.06 (1.0)	0.93 (1.3)	-0.03 (1.4)	-0.03 (0.9)
Gestational age, mean (SD), weeks	39.0 (1.8)	40.0 (1.9)	39.8 (1.5)	39.0 (1.5)	38.7 (3.2)	40.0 (1.3)
Small for gestational age, n (%)	0 (0)	3 (6.8)	5 (1.8)	1 (2.7)	12 (11.0)	3 (1.1)
Large for gestational age, n (%)	18 (11.7)	4 (9.1)	6 (2.1)	8 (21.6)	6 (5.5)	4 (1.5)
Male, n (%)	82 (53.2)	25 (56.8)	138 (49.1)	22 (59.5)	52 (47.7)	120 (45.1)

Current characteristics						
Age, mean (SD), years	23.0 (1.2)	23.6 (1.0)	23.6 (1.1)	25.0 (0.6)	25.3 (0.6)	25.3 (0.6)
Daily smoking, n (%)	40 (26.0)	12 (27.3)	55 (19.6)	15 (40.5)	40 (36.7)	85 (32.0)
Body mass index ≥ 25kg/m^2, n (%)	64 (41.6)	23 (52.3)	83 (29.5)	18 (48.6)	52 (47.7)	73 (27.4)
Body mass index ≥ 30kg/m^2, n (%)	19 (12.3)	1 (2.3)	21 (7.5)	6 (16.2)	20 (18.3)	19 (7.1)
Abdominal obesity[b]						
Men with waist circumference >94cm, n (%)	26 (31.7)	6 (24.0)	18 (13.0)	5 (22.7)	19 (36.5)	20 (16.7)
Women with waist circumference >80cm, n (%)	24 (33.3)	7 (36.8)	33 (23.1)	10 (66.7)	26 (45.6)	35 (24.0)
Parental education, n (%)						
Basic	22 (14.3)	6 (13.6)	12 (4.3)	6 (16.2)	15 (13.8)	18 (6.8)
Secondary	84 (54.5)	25 (56.8)	168 (59.8)	17 (45.9)	54 (49.5)	104 (39.1)
Lower-level tertiary	15 (9.7)	7 (15.9)	36 (12.8)	0 (0)	12 (11.0)	30 (11.3)
Upper-level tertiary	32 (20.8)	6 (13.6)	61 (21.7)	13 (35.1)	21 (19.3)	103 (38.7)

ESTER, Maternal Pregnancy Disorders and Early-Life Programming of Adult Health and Disease

AYLS, Arvo Ylppö Longitudinal Study

[a] Pre-pregnancy body mass index ≥ 25kg/m^2

[b] International Diabetes Federation criteria for Europid population values for waist circumference, World Health Organization cut-off point for risk of metabolic complications

Table 2. Body size and body composition of young adults born to mothers with gestational diabetes, pre-pregnancy obesity or overweight and their controls, i.e. offspring of normoglycemic mothers with normal pre-pregnancy weight, with data presented separately for two birth cohort studies.

	ESTER cohort (n=479)			AYLS cohort (n=412)			
Characteristic	Maternal gestational diabetes (n=154)	Maternal pre-pregnancy obesity or overweight [a] (n=44)	Control (n=281)	Maternal gestational diabetes (n=37)	Maternal pre-pregnancy obesity or overweight [a] (n=109)	Control (n=266)	Mean in Finnish population[b] /Reference
Height (SD), cm							
Women	165.5 (5.9)	164.1 (3.9)	163.9 (6.2)	167.8 (8.0)	165.0 (7.1)	166.5 (6.0)	165.9 (0.1)
Men	178.3 (6.3)	179.0 (6.8)	178.0 (7.2)	181.6 (7.8)	180.5 (6.6)	180.0 (6.3)	179.6 (0.1)
Body mass index (SD), kg/m^2							18.5-24.9
Women	23.9 (4.2)	23.6 (3.3)	23.2 (4.4)	25.7 (4.4)	25.1 (5.0)	22.8 (4.1)	24.0 (4.3)
Men	26.2 (4.8)	25.5 (3.6)	24.0 (3.3)	24.7 (4.6)	26.9 (5.3)	24.1 (3.8)	25.9 (4.2)
Waist circumference (SD), cm							<80/<94[c]
Women	77.7 (10.4)	75.9 (6.0)	74.9 (9.6)	85.2 (11.0)	81.7 (12.2)	76.2 (9.7)	77.2 (95% CI 76.3-78.2)
Men	88.9 (12.5)	87.3 (8.5)	82.9 (8.3)	87.3 (12.1)	92.9 (13.6)	85.8 (9.8)	89.8 (95% CI 88.9-90.7)
Lean body mass (SD), kg							

Women	45.6 (6.0)	44.8 (4.2)	44.5 (5.6)	50.4 (7.6)	46.5 (5.6)	46.0 (5.4)	
Men	65.6 (9.3)	64.7 (8.0)	62.9 (9.0)	66.4 (9.6)	68.8 (9.4)	64.6 (8.9)	
Fat mass (SD), kg							
Women	19.9 (8.0)	18.9 (6.1)	17.9 (8.6)	22.5 (9.4)	21.8 (10.1)	17.3 (8.3)	
Men	17.9 (10.1)	16.7 (7.7)	13.2 (5.9)	15.1 (9.6)	19.0 (11.1)	13.4 (6.5)	
Fat percentage (SD), %							16-30/11-20[c]
Women	29.4 (6.8)	28.9 (6.8)	27.7 (7.5)	29.8 (8.3)	30.6 (8.4)	26.3 (7.3)	28.5 (7.8)
Men	20.3 (7.4)	19.8 (6.3)	16.9 (5.7)	17.7 (7.2)	20.5 (8.1)	16.6 (5.4)	19.9 (6.0)

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[a] Pre-pregnancy body mass index ≥ 25kg/m^2

[b] Adults aged 25-34 years, FINRISK study 2012, http://urn.fi/URN:ISBN:978-952-302-054-2

[c] women / men

Table 3. Body size and composition of young adult offspring of mothers with gestational diabetes compared with controls (comprising offspring of normoglycemic mothers with normal pre-pregnancy weight) and offspring of mothers with pre-pregnancy obesity or overweight compared with controls. The results are presented as mean differences (95% confidence intervals).

Characteristic		Women				Men			
	Model	Maternal gestational diabetes n 87 vs. 289 controls	P-value	Maternal pre-pregnancy obesity or overweight [a] n 76 vs. 289	P-value	Maternal gestational diabetes n 104 vs. 258	P-value	Maternal pre-pregnancy obesity or overweight [a] n 77 vs. 258	P-value
Height (SD), cm	1	1.38 (-0.20, 2.97)	0.087	-0.80 (-2.39, 0.79)	0.320	0.86 (-0.79, 2.50)	0.303	-0.73 (-1.07, 2.53)	0.424
	2	-0.10 (-1.80, 1.59)	0.905	-1.22 (-2.91, 0.47)	0.157	-0.61 (-2.32, 1.11)	0.484	-0.17 (-1.98, 1.64)	0.854
Body mass index (SD), kg/m^2	1	1.26 (0.16, 2.36)	0.025	1.67 (0.56, 2.78)	0.003	1.75 (0.81, 2.69)	<0.001	2.35 (1.34, 3.36)	<0.001
	2	0.82 (-0.39, 2.04)	0.185	1.41 (0.20, 2.63)	0.023	0.88 (-0.17, 1.92)	0.099	1.64 (0.57, 2.72)	0.003
Waist circumference (SD), cm	1	4.56 (2.03, 7.10)	<0.001	4.05 (1.51, 6.59)	0.002	4.86 (2.46, 7.27)	<0.001	5.44 (2.90, 7.99)	<0.001
	2	3.39 (0.60, 6.18)	0.017	3.09 (0.35, 5.83)	0.027	2.63 (-0.01, 5.28)	0.051	3.34 (0.68, 5.99)	0.014
Lean body mass (SD), kg	1	1.73 (0.24, 3.22)	0.023	0.56 (-0.85, 1.97)	0.437	2.47 (0.31, 4.62)	0.025	3.37 (1.05, 5.70)	0.005
	2	0.09 (-1.49, 1.67)	0.915	-0.15 (-1.67, 1.37)	0.849	-0.11 (-2.34, 2.11)	0.920	1.66 (-0.63, 3.94)	0.155
Fat mass (SD), kg	1	2.93 (0.78, 5.08)	0.008	3.18 (0.98, 5.39)	0.005	3.89 (2.11, 5.67)	<0.001	4.78 (2.89, 6.68)	<0.001
	2	2.15 (-0.24, 4.54)	0.078	2.84 (0.43, 5.26)	0.021	2.39 (0.41, 4.37)	0.018	3.43 (1.42, 5.43)	0.001

Fat percentage (SD), %	1	2.50 (0.62, 4.38)	0.009	3.11 (1.17, 5.05)	0.002	2.81 (1.34, 4.28)	<0.001	3.52 (1.92, 5.11)	<0.001
	2	2.32 (0.24, 4.41)	0.029	2.98 (0.87, 5.09)	0.006	1.97 (0.32, 3.61)	0.019	2.70 (0.99, 4.41)	0.002

Linear regression models as follows:
Model 1 adjusted for age and cohort
Model 2 adjusted for age, cohort, gestational age, birth weight SD score, maternal hypertension or preeclampsia during pregnancy, maternal smoking during pregnancy and parental educational attainment
[a] Pre-pregnancy body mass index ≥ 25kg/m^2

Table 4. Body size and composition of young adults, all born to mothers with gestational diabetes; separately comparing offspring of mothers with normal pre-pregnancy weight and offspring of mothers with pre-pregnancy overweight or obesity, with controls comprising offspring of normoglycemic mothers with normal pre-pregnancy weight. The results are presented as mean differences (95% confidence intervals).

Characteristic		Women				Men			
	Model	Maternal gestational diabetes, normal pre-pregnancy weight [a] n 54 vs. 289 controls	P-value	Maternal gestational diabetes, pre-pregnancy obesity or overweight [b] n 30 vs. 289 controls	P-value	Maternal gestational diabetes, normal pre-pregnancy weight [a] n 63 vs. 258 controls	P-value	Maternal gestational diabetes, pre-pregnancy obesity or overweight [b] n 42 vs. 258 controls	P-value
Height (SD), cm	1	1.31 (-0.56, 3.19)	0.170	1.60 (-0.88, 4.07)	0.205	1.17 (-0.84, 3.18)	0.251	0.40 (-1.93, 2.73)	0.737
	2	0.09 (-1.93, 1.95)	0.993	-0.85 (-3.60, 1.89)	0.370	0.42 (-1.59, 2.42)	0.457	-3.38 (-5.95, -0.82)	0.010
Body mass index (SD), kg/m^2	1	0.67 (-0.62, 1.95)	0.307)	2.39 (0.66, 4.11)	0.007	0.69 (-0.36, 1.75)	0.198	3.34 (2.04, 4.64)	<0.001
	2	0.12 (-1.26, 1.49)	0.869	2.53 (0.55, 4..52)	0.013	0.47 (-0.65, 1.60)	0.406	1.78 (0.26, 3.30)	0.002
Waist circumference (SD), cm	1	3.26 (0.34, 6.18)	0.029	7.01 (3.06, 10.96)	0.001	2.87 (0.15, 5.60)	0.039	7.96 (4.68, 11.24)	<0.001
	2	1.83 (-1.26, 4.92)	0.244	6.52 (1.97, 11.07)	0.005	2.49 (-0.40, 5.38)	0.091	3.21 (-0.56, 6.98)	0.095
Lean body mass (SD), kg	1	1.05 (-0.68, 2.78)	0.232	2.96 (0.66, 5.26)	0.012	1.54 (-1.06, 4.13)	0.245	4.15 (1.12, 7.18)	0.007
	2	-0.58 (-2.35, 1.19)	0.522	1.35 (-1.22, 3.92)	0.303	0.36 (-2.21, 2.93)	0.785	1.57 (-4.86, 1.71)	0.347
Fat mass (SD), kg	1	1.79 (-0.73, 4.32)	0.164	5.11 (1.75, 8.48)	0.003	1.74 (-0.14, 3.61)	0.069	6.89 (4.43, 9.34)	<0.001

	2	0.83 (-1.87, 3.54)	0.546	5.22 (1.33, 9.11)	0.009	1.57 (-0.43, 3.57)	0.123	4.24 (1.36, 7.11)	0.004
Fat percentage (SD), %	1	1.77 (-0.47, 4.02)	0.122	4.17 (1.26, 7.08)	0.005	1.30 (-0.35, 2.95)	0.123	4.86 (2.81, 6.92)	<0.001
	2	1.41 (-0.99, 3.81)	0.248	4.69 (1.34, 8.03)	0.006	1.29 (-0.48, 3.05)	0.305	3.66 (1.24, 6.09)	0.003

Linear regression models as follows:
Model 1 adjusted for age and cohort
Model 2 adjusted for age, cohort, gestational age, birth weight SD score, maternal hypertension or preeclampsia during pregnancy, maternal smoking during pregnancy and parental educational attainment
[a] Pre-pregnancy body mass index < 25kg/m^2
[b] Pre-pregnancy body mass index ≥ 25kg/m^2